

Ion Hydration Studies Aimed at Ion Channel Selectivity

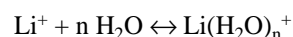
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Cell membranes contain water-filled pores called ion channels that pass millions of ions per second between the cell exterior and interior. The movement of ions through these channels controls excitation and electrical signaling in the nervous system. One of the most remarkable properties of ion channels is their ability to distinguish between ions. Potassium ion channels, for instance, preferentially conduct K^+ over Na^+ ions by a ratio of over 14:1. With regard to size, charge, and concentration gradients between the external and internal cell solutions, Na^+ ions appear nearly identical to K^+ ions. How then do ion channels distinguish between ions?

Recent simulation studies provide clues to the important issues that establish ion channel selectivity. In model potassium channels, the hydrated ion must diffuse up to the pore and

lower energy for a tetrahedral structure than for structures with six water molecules in the innermost hydration shell. Molecular simulation studies produce a range of results including both four and six inner shell hydration structures.

To resolve the question of hydration structure and energetics [1], we have applied the quasi-chemical theory of liquids to $Li^+(aq)$ ion [2]. The first step is the study of the hydration reactions



that combine n water molecule ligands with the Li^+ ion in a geometrically defined inner sphere under ideal gas conditions. At a subsequent step an approximate, physical description of

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lose part of its hydration shell in exchange for backbone carbonyl groups from the channel wall, as illustrated in Figure 1. The striking difference between the transport of Na^+ and K^+ ions through the model pore apparently centers around the hydration state of the ion. The ion with fewer waters attached to it, the K^+ ion, enters deeper into the pore. Thus, according to simulation studies, both the hydration state of the ion and its propensity to exchange its water ligands for carbonyl groups play a crucial role in determining ion channel selectivity.

The first aim of our research on ion channel selectivity is to secure an understanding of the inner hydration structures and energetics of the alkali metal ions. Currently our knowledge of hydration for even the simplest alkali metal ion, Li^+ , is incomplete. For example, some interpretations of neutron and X-ray scattering measurements on $LiCl$ solutions in liquid water suggest that the Li^+ ion carries six water molecules in its first hydration shell. In contrast, spectroscopic studies claim tetrahedral coordination for the Li^+ ion in water. On the theoretical side, electronic structure calculations on the Li^+ ion with six water molecules predict a slightly, but distinctly,

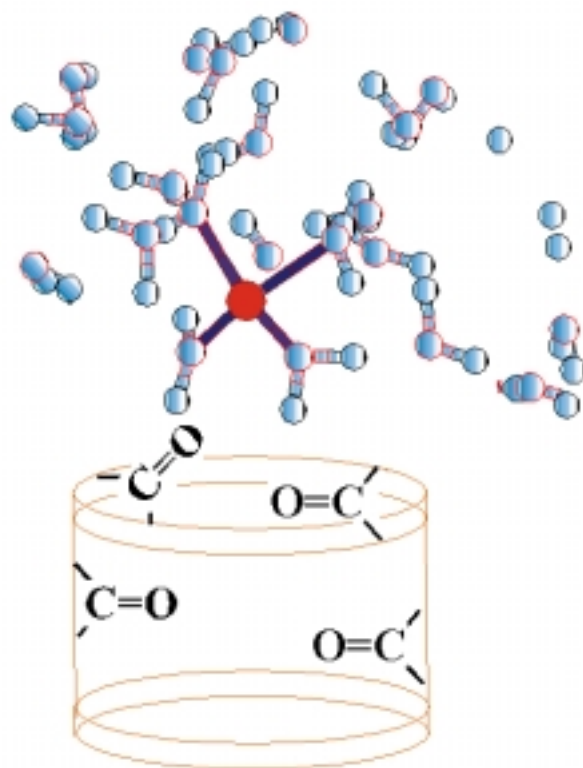


Figure 1.

the aqueous environment surrounding these complexes is included. By considering only those reactions that form inner sphere products, we can treat the inner ligands explicitly, in

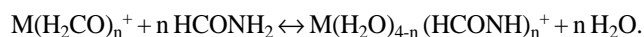
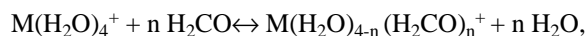
molecular detail using quantum mechanics, and at the same time achieve a description of outer sphere hydration thermodynamics that is consistent from one complex to another.

Our quasi-chemical results predict that the $n = 4$ hydration complex is most probable in liquid water at room temperature and atmospheric pressure. With quasi-chemical theory, we can calculate the absolute hydration free energy of the Li^+ ion under the same ambient conditions. The theoretical result predicts an absolute hydration free energy of -128 kcal/mol , which falls within ten percent of the experimental values for the $\text{Li}^+(\text{aq})$.

To further test the $n = 4$ prediction, we performed 'ab initio' molecular dynamics calculations. In this classical simulation, the full anharmonic forces are determined by solving the electronic Schrödinger equation at each simulation step. The system, consisting of one Li^+ ion and 32 water molecules in periodic boundary conditions, relaxed from the initial $n = 6$ structure to stable $n = 4$ alternatives within 1 ps, as depicted in Figure 2.

The 'ab initio' molecular dynamics and the quasi-chemical theory of liquids exploit different approximations and produce the same conclusion here. This *agreement* supports the prediction that $\text{Li}^+(\text{aq})$ has four inner shell water ligands at infinite dilution in liquid water under normal conditions. This prediction currently differs from interpretations of neutron and X-ray scattering data on aqueous solutions.

What about the Na^+ and K^+ ions and the potassium ion channel? Preliminary results using quasi-chemical theory suggest an underlying thermodynamic basis for distinction between the ions. In this study, the free energy changes for exchange of an inner shell water ligand with n formaldehyde or formamide molecules were calculated for the situation in which both alkali metal ions bind a maximum of four inner shell ligands.



The reaction free energy change plotted in Figure 3 shows barriers to both $\text{Na}^+(\text{aq})$ and $\text{K}^+(\text{aq})$ for exchange of inner shell waters with formaldehyde molecules, but favorable wells for exchange with formamide molecules. Apparently, formamide better models a protein carbonyl group that facilitates ion transport through a channel. According to our results, a protein carbonyl group with the structure of formamide stabilizes both ions and replaces their first inner shell water molecules with equal favor. Subsequent

replacement of inner shell water molecules is thermodynamically more favorable for $\text{Na}^+(\text{aq})$ than $\text{K}^+(\text{aq})$. This suggests that Na^+ may stick to the ion channel wall, while K^+ ion passes through the channel more easily. Certainly a substantial contribution to ion channel selectivity arises from thermodynamic features of exchange between the hydrated ion ligands and carbonyl groups on the ion channel wall.

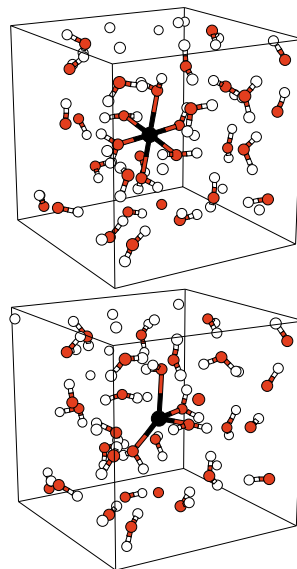


Figure 2.

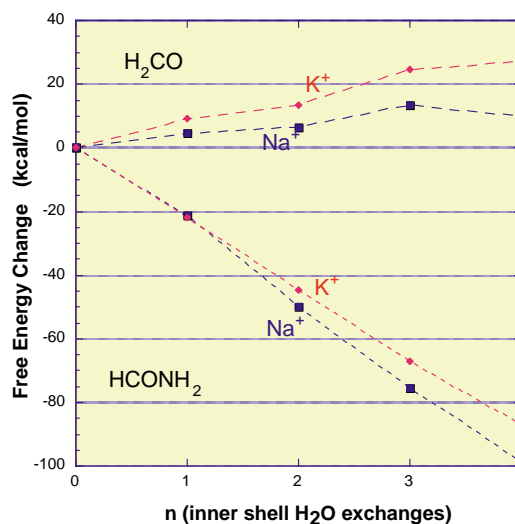


Figure 3.

[1] Rempe, S. B.; Pratt, L. R.; Hummer, G.; Kress, J. D.; Martin, R. L.; Redondo, A. *J. Am. Chem. Soc.* **122**, 5 (2000).

[2] Pratt, L. R.; Rempe, S. B. **Simulation and Theory of Electrostatic Interactions in Solution**, eds. L. R. Pratt and G. Hummer: (AIP, New York, 1999) p. 172.

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